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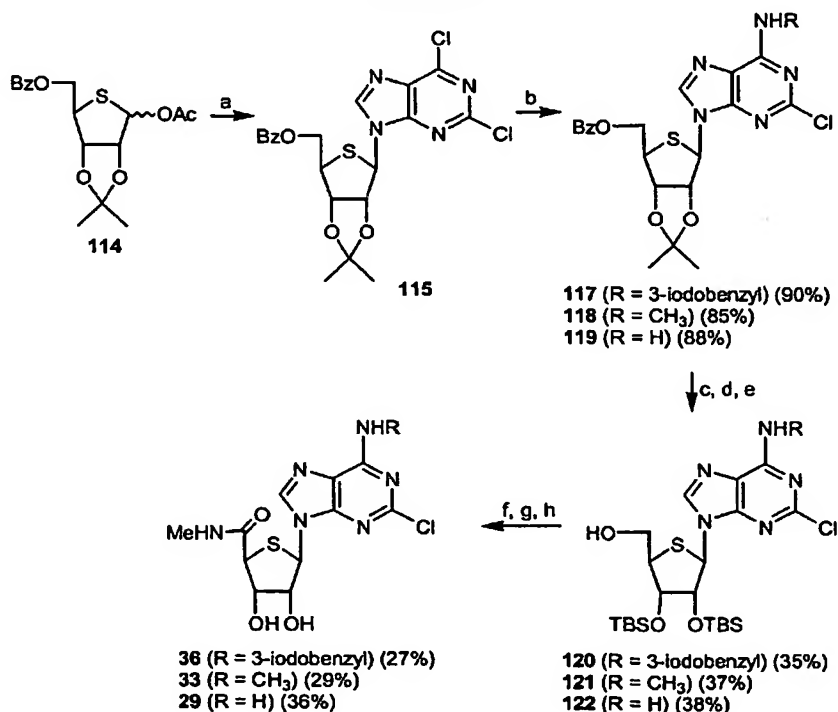
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[Continued on next page]

(54) Title: PURINE NUCLEOSIDES

Scheme 2



Reagents: a) silylated 2,6-dichloropurine, TMSOTf; b) RNH₂; c) 80% AcOH; d) TBSCl, DMF; e) NaOMe, MeOH; f) i. PDC, DMF, ii. K₂CO₃, (CH₃O)₂SO₂; g) 40% MeNH₂, MeOH; h) *n*-Bu₄NF, THF.

(57) Abstract: Disclosed are purine nucleoside compounds that are selective to A₃ adenosine receptors and are useful for the treatment of cancer and inflammatory diseases. The compounds are shown by the following general formula (I), including isomers thereof: wherein X is sulfur or oxygen; R₁ is hydrogen, alkyl, benzyl, halobenzyl, or phenylalkyl; R₂ is hydrogen, halogen, alkoxy, alkenyl, alkynyl, alkylthio, or thio; R₃ and R₃' are hydrogen, hydroxyalkyl, alkoxyalkyl, or alkylaminocarbonyl, whereas R₃ and R₃' do not have identical substituents simultaneously; and R₄ is hydrogen or alkyl. Also disclosed are a pharmaceutical composition comprising a compound of formula (I), an isomer, or its pharmacologically acceptable salt as an active ingredient and a method for preventing or treating various diseases, state, or condition, including asthma, inflammation, cerebral ischemia, heart diseases, and cancer.

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(81) **Designated States (national):** AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/33987

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07H 19/167, 19/16; C07D 473/34, 473/18; A61K 31/52; 31/522 A61P 35/00, 29/00
 US CL : 536/27.62, 27.63, 27.7, 27.6, 27.22; 544/276, 277; 514/45, 46, 263.23

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/27.62, 27.63, 27.7, 27.6, 27.22; 544/276, 277; 514/45, 46, 263.23

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
 CAS Online

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BOULLAIS et al. Synthèse, structure et réactivité de selenoxydases dérivées du ribose et de l'adénosine: Nouvelle voie d'accès aux ribofuranosides insaturés en C(4')-C(5').	1,3
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A	Tetrahedron. 1983, Vol. 39, No. 5, pages 759-765. See 15	2, 4-9
X	MCCORMICK et al. Thio sugars part 9. Antiviral nucleosides from 4-thio-dl-erythrofuranoose and purines and other fused pyrimidines. Proceedings of the Royal Academy of Sciences. 1983, Vol. 83B, pages 125-138. See 9a.	1, 2, 4, 6, 8
X	MCCORMICK et al. Thio-sugars. Part 3. 4-Thiotetrafuranose nucleosides. J.C.S. Perkins I. 1978, Vol. 5, pages 500-505. See 2c.	1, 2, 4, 6, 8
X	JACOBSON et al. Structure-Activity Relationships of 9-Alkyladenine and Ribose-Modified Adenosine Derivatives at Rat A3 Adenosine Receptors. J. Med. Chem. 1995, Vol. 38, pages 1720-1735. See 1, 2, 25, 28, 39, 40 and "adenosine" itself.	1, 3
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Y		2, 4-9
X	US 5,688,774 A (JACOBSON) 18 November 1997. See example 17	1, 3
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Y		2, 4-9

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/33987

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claim Nos.: 10-16
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☐

- The additional search fees were accompanied by the applicant's protest.
No protest accompanied the payment of additional search fees.

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